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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,221	10/16/2003	Arnold E. Ruoho	096429-9146	9468

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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 12/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,221	RUOHO ET AL.	
	Examiner	Art Unit	
	Michael Brannock	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *none* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *020904*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Priority

It is noted that this application appears to claim subject matter disclosed in prior Application No. 09389835 and 60/098950, filed 09/03/1999 and 09/03/1998, respectively. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim

filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Claim Objections

Claim 11 is objected to because of the following informalities: it appears that the word "of" is missing between the words "step" and "culturing" in line 3 of the claim. Additionally it appears that the word "a" is missing between "having" and "bacteriorhodopsin" in line 7. Also, part (a) of claim 13 is garbled in the first three lines. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims require that a portion of bacteriorhodopsin is replaced with the structurally analogous region of a G-protein coupled receptor protein. The phrase "structurally analogous region" renders the claims indefinite because the specification does define not set forth a definition of this phrase that the skilled artisan could use to determine what is and what is not encompassed by the claims, see page 10. While it is acknowledged that bacteriorhodopsin is famous as a template to construct three dimensional models of G-protein coupled receptors (GPCRs), see Hoflack *et al., Trends in Pharm. Sci.* 15:7-9, 1994, especially col. 1 of page 7, the art is equivocal as to the precise structural relationships between bacteriorhodopsin and G-protein coupled receptors. For example, Pardo *et al., PNAS* 89:4009-4012, 1992 teach that the transmembrane regions, in particular, of bacteriorhodopsin and G-protein coupled receptors, do

not correspond to each other. Further, Sohlemann *et al. Naunyn Schmiedebergs Archives of Pharm.* 355(2)150-160, 1997 acknowledge that available structural data suggest that bacteriorhodopsin and rhodopsin (a GPCR) share overall topology, however there are clear differences in the packing of the helices. In the present state it is not clear what types of relationship[s] exist between bacteriorhodopsins and GPCRs", see page 151 first col. Thus, one of skill in the art could not rely on the prior art to know, unambiguously, which structures are analogous between bacteriorhodopsin and GPCRs, as would be required to establish the bounds of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No: 5641650.

U.S. Patent No: 5641650 discloses a chimeric fusion protein comprising a bacteriorhodopsin protein amino acid sequence (signal sequence or C-terminal, see col 2) which at least a portion of the protein (e.g. the remaining parts of the protein) are replaced with the structurally analogous region of a G-protein receptor (e.g. serotonin receptor, see col 8). U.S. Patent No: 5641650 further disclose methods of producing the protein comprising culturing an

archaebaterium comprising the construct encoding the protein connected to a promoter sequence functional in the archaebacterium under suitable condition and for a period time sufficient to allow expression of the chimeric fusion protein and then partially purifying the chimeric fusion protein, see cols 11 and 12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Popot *et al.*, *Current Opinion in Biotechnology* 6:394-402, 1995, U.S. Patent No: 5641650, Hoflack *et al.*, *Trends in Pharm. Sci.* 15:7-9, 1994 and Teufel *et al., EMBO Journal, 12(9)3399-3408, 1993*, in view of Okamoto *et al.*, Cell 67(723-730)1991.

Popot *et al.* suggest that chimeric constructs of bacteriorhodopsin and of G-protein receptors can be made for the purposes of functional and structural investigations (pg 396 col 1); that bacteriorhodopsin "can be used as a 'bench top' on which to arrange engineered loops that are designed to form binding or catalytic sites (pg 397 col. 2), and that a wealth of data indicates that most of the six loops connecting the transmembrane helices in bacteriorhodopsin can be tampered with to large extents and at least three of them can be cut without preventing refoloding of the proteins (e.g. cytoplasmic loop III, reference 61 Teufel *et al*) (pg 397 col. 2). Further, the use of archaebacteria for recombinant expression of bacteriorhodopsin/GPCRs chimeras is well

established in the art, as disclosed in U.S. Patent No: 5641650, e.g. col 4, L46 . Further, it is old and well established in the art that bacteriorhodopsin is famous as a template to construct three dimensional models of G-protein coupled receptors (GPCRs), see Hoflack *et al., Trends in Pharm. Sci.* 15:7-9, 1994, especially col. 1 of page 7. Teufel *et al.* teach that the protein architecture of bacteriorhodopsin (BR) "suggests the possibility of using BR as a structural scaffold in the construction of biological membranes with new and pre-defined properties by replacing the extra-membrane parts of BR with exogenous polypeptide modules of known function", see col 2 of page 3399. Additionally, Teufel et al. teach that the "structural integrity of loops B/C, CD, D/E, and E/F (E/F is the third cytoplasmic loop) is not a prerequisite of BR function and that the construction of multi functional proteins on the basis of BR as a structural scaffold is a feasible proposition. Loops B/C, CD, D/E and E/F are now clearly identified as prime candidates for future constructions of more complex loop replacements" see the last paragraph of page 3405. Additionally, Teufel *et al.* define what residues are to be considered the third cytoplasmic loop, see Fig 1, which correspond exactly to amino acids 171-179 of the instant SEQ ID NO: 2. Okamoto *et al.* teach that peptides corresponding to the third cytoplasmic loop of a GPCR, e.g. the human β-adrenergic receptor, can activate G- protein, see the Abstract. Furthermore, Hoflack et al., teaches that "the relevance of the use of BR as a template to model G-protein coupled receptors must be determined since this approach is used at present by most pharmaceutical companies and some academic laboratories to rationalize their drug design. Thus Okamoto and Hoflack point to the desirability of finding drugs that interact with intercellular loop 3 using GTP exchange assays that are old and well established in the art, as required by claims 13 and 14 using GTP.

Therefore, it would be obvious to one of ordinary skill in the art, with reasonable expectation of success to construct chimeric bacteriorhodopsin/ GPCRs, as taught U.S. Patent No: 5641650 and suggested by Popot *et al.* and Teufel *et al.* using regions that are structurally analogous between GPCRs and bacteriorhodopsin, as is well established in the art (see Hoflack et al.), particularly that of the third intracellular loop of the human β-adrenergic receptor as taught by Okamoto *et al.* The motivation to do so is provided by Popot *et al.* who teach that bacteriorhodopsin "can be used as a 'bench top' on which to arrange engineered loops that are designed to form binding or catalytic sites (pg 397, col 2) and by Okamoto *et al.* who teach the third intracellular loop of the human β-adrenergic receptor provides for binding and activation of G-proteins, and who also teach the need for further study of the structure and function of the third intracellular loop of the human β-adrenergic receptor as is well appreciated in the art, e.g. see Introduction and Discussion. Further, the construction of a bacteriorhodopsin chimera at amino acids 171-179 (intracellular loop III) is suggested by Teufel who show these residues to define the cytoplasmic loop III, see Figure 2.

Additional Reference:

The following reference is considered relevant to the instant Application but is not being relied upon to support any of the rejections above:

Kenakin-T, *Pharmacological Reviews* 48(3)413-462, 1996, teaches that the ability of short peptides, comprising the third intracellular loop of a GPCR, to activate a G-protein appears to be a general property of GPCRs, see the paragraph bridging pages 435 and 436.

Conclusion

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.

Please note the new central fax number for official correspondence below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (571) 272-0869. The examiner can normally be reached on Mondays through Fridays from 10:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867. Official papers filed by fax should be directed to **571-273-8300**.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Elizabeth C. Kemmerer

MB

ELIZABETH KEMMERER
PRIMARY EXAMINER

November 28, 2005